Drugs and diseases

Summary and consensus statements of group 1. The 5th EAO Consensus Conference 2018

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SUPPLEMENT ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

Drugs and diseases: Summary and consensus statements of group 1. The 5th EAO Consensus Conference 2018

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[Correction added on 7 December 2018, after first online and print publication: the author Luis Miguel Sánchez Suárez and his affiliation have been added in this current version.]

Abstract

Objectives: The task of this working group was to update the knowledge about the use of drugs and biologicals affecting healing of soft tissue and bone during implant treatment or procedures associated with it. Moreover, the impact of titanium particles and biocorrosion on complications and implant survival has been analysed.

Materials and Methods: The literature in the areas of interest (platelet concentrates, antiresorptive drugs as well as implant–host interaction) was screened using systematic reviews for the former two areas, whereas a narrative critical review was performed for the latter topic. Two manuscripts on platelet concentrates, one manuscript on antiresorptive drugs and one manuscript on the effects of biocorrosion, were presented for group analysis with subsequent discussion in the plenum and final consensus approval.

Results: Results and conclusions of the individual reviews of the three topics are presented in the respective papers. Conclusions of the group on strengths and

weaknesses of available evidence as well as consensus statements and directions for further research are provided in this study.

The following papers were subject to group discussions and formed the basis for the consensus statements:

Stähli A, Strauss FJ, Gruber R. (2018) The use of platelet-rich-plasma to enhance the outcomes of implant-related therapies: a systematic review

Strauss FJ, Stähli A, Gruber R. (2018) The use of platelet-rich-fibrin to enhance the outcomes of implant-related therapies: a systematic review

Mombelli A, Hashim D, Cionca N. (2018) What is the impact of titanium particles and bio-corrosion on implant survival and complications? A critical review

Stavropoulos A, Bertl K, Pietschmann P, Pandis N, Morten Schiødt, Klinge B. (2018) The effect of antiresorptive drugs on implant therapy: a systematic review.

KEYWORDS

alveolar ridge preservation, antiresorptive drugs, bisphosphonates, corrosion, dental implants, guided bone regeneration sinus floor elevation, hormone replacement therapy, implant therapy, medication-related osteonecrosis of the jaws, peri-implantitis, platelet-rich fibrin, platelet-rich plasma, systematic review, titanium

1 | THE USE OF PLATELET PREPARATIONS TO ENHANCE THE OUTCOMES OF IMPLANT-RELATED THERAPIES: A SYSTEMATIC REVIEW

Platelet concentrates (PCs) are blood extracts, obtained after processing a whole blood sample through centrifugation. Different techniques leading to a variety of preparations have been developed. For the preparation of platelet-rich plasma (PRP) and plasma rich in growth factors (PRGF), citrated blood is used during the centrifugation process to avoid coagulation. This results in liquid PRP and PRGF. For the use in gel form, thrombin and/or calcium chloride is added to induce fibrin polymerization creating a weak fibrin network. For the preparation of platelet-rich fibrin (PRF), no anticoagulant and no thrombin/calcium chloride is used and only one step of centrifugation is employed during which coagulation occurs.

1.1 | Focus question

Is there any additional benefit from the use of PCs over traditional approaches in terms of clinical and radiographic outcomes in implant therapy including implant placement as well as associated procedures such as ridge preservation, ridge augmentation, sinus floor augmentation and treatment of peri-implantitis?

1.2 | Summary

1.2.1 | Dental implant placement

Coating of implants with **PRP** during implant insertion has shown no benefits *(1 Randomized Clinical Trial -RCT- & 1 Controlled Clinical trial –CCT-, 40 patients, High Risk of Bias -HRB)*. The coating of implants with **PRF** before or during implant insertion has shown a significant increase in Implant Stability Quotient ISQ values. (2-12 ISQ units, 6 weeks)*(2 RCTs, 40 patients, 104 implants, Unclear or Low Risk of Bias URB-LRB)*. The use of **PRF** membranes in conjunction with implant placement to cover the bone before tissue closure have shown less bone loss during the first three months (0.35 mm) *(1 RCT, 20 patients., URB)*.

1.2.2 | Ridge preservation

This question was answered separately for the use of PCs alone compared to no treatment and the use of grafting materials with/without PCs.

Use of PCs alone

For the use of **PRP,** no data have been reported in the reviewed paper on the reduction in bone resorption but improved soft tissue healing was observed compared to no treatment *(1 RCT, 23 patients, LRB)*. When **PRGF** was used for alveolar preservation, no benefits have been shown *(1 CCT, 28 patients, HRB)*. The use of **PRF** after dental extraction with a flapless approach has shown to provide less alveolar resorption and an increased bone fill at three months *(2.1 mm -29%- less horizontal ridge resorption, 30% more socket filling) (1 RCT, 22 patients, LRB)* and is associated with improved soft tissue healing at one week *(1 RCT, 26 p., URB)* compared to no treatment.

Use of PCs in combination with grafting materials:

No benefits have been reported when **PRP** was used in combination with decalcified freeze-dried bone allograft (DFDBA) as alveolar

filling material *(1 RCT, 53 patients, URB)*. **PRF** used in combination with DFDBA and a collagen membrane improved horizontal ridge preservation (0.61 mm) *(1 RCT, 36 patients, URB)*. **PRF** used in combination with autogenous bone has shown no significant clinical benefits *(1 RCT, 12 patients, URB)*.

1.2.3 | Ridge augmentation

The use of **PRP** during ridge augmentation procedures has shown benefits with respect to crest width (0.3-0.4 mm) and height (0.4 mm) *(2 RCTs, 62 patients, LRB)* and higher soft tissue stability showing significantly less graft exposures (28%). The addition of **PRF** to a synthetic graft material in ridge augmentation has shown no benefits *(1 RCT, 82 patients, URB)*.

1.2.4 | Sinus floor augmentation

No RCTs or CCTs evaluating the sinus floor augmentation with **PRF, PRP** or **PRGF** alone have been identified.

The addition of **PRP** to autologous bone has shown no benefits in terms of implant survival rate, implant stability, augmentation height, marginal bone level changes, bone density, volume of lamellar and woven bone, volume of new bone, bone graft resorption, angiogenesis and soft tissue healing *(5 RCT, 2 CCT, 167 patients, LRB-HRB)*. Some papers reported short-term improvement on outcome measures related to bone formation and densitometric values *(2 RCTs and 1 CCT, 81 patient, URB)*. The clinical relevance of these parameters is unclear. The use **PRP** in combination with β-TCP *(1 RCT, 35 p., URB)* or xenografts *(2 RCTs, 1 CCT, 127 patients, URB-LRB)* has shown no clinical benefits.

The use of **PRF** in combination with deproteinized bovine bone mineral (DBBM) has shown no additional benefits (2 RCTs, 73 patients, LRB).

1.2.5 | Surgical treatment of peri-implantitis

No RCTs/CCTs on the use of PRP / PRGF in treatment of peri-implantitis were found. The use of **PRF** in open flap debridement has shown improvement on soft tissue-related parameters such as probing depth reduction (0.5 mm), clinical attachment gain (1.4 mm) and reduction in peri-implant soft tissue recession (0.9 mm) *(1 RCT, 19 patients, URB)*.

1.3 | Consensus statements

The RCTs and CCTs included in this review were short-term (mainly between 3 weeks and 6 months) and the great majority of them had small sample sizes with no sample size calculation described. Conclusion on individual procedures analysed is based mostly on one or two RCTs. Given the limitation with the large majority of included studies being underpowered, the resulting evidence hence is still weak and has to be considered with caution.

The use of **PRP** has been reported to be **beneficial**:

- during alveolar ridge augmentation procedures by increasing ridge width and height as well as reducing the rate of graft exposure (2 RCTs).

The use of **PRP** has shown **no benefits**:

- as sole material or in combination with DFDBA in alveolar ridge preservation (2 RCTs),
- during implant placement with respect to implant stability and marginal bone loss (1 RCT, 1 CCT).
- in sinus lift techniques when used in combination with bone or bone substitutes (10 RCTs, 4 CCTs)

The use of **PRGF** has not shown benefits for ridge preservation and has not been evaluated in other indications.
The use of **PRF** has been reported to be **beneficial**:

- as sole material or in combination with non-autogenous grafting material in limiting post-extraction alveolar ridge resorption (3 RCTs). The beneficial effect of PRF in combination with grafting material vs. graft material alone is substantially smaller than the use of PRF alone vs. no treatment.
- during implant placement by improving early implant ISQ values (2 RCTs) and reducing early marginal bone loss (1 RCT).
- in open flap debridement in peri-implantitis treatment by improving clinical attachment levels, and reducing marginal tissue recession and probing pocket depth (1 RCT).

The use of **PRF** has shown **no benefits**:

- in sinus lift techniques when used in combination with autogenous bone or bone substitutes (2 RCTs)

1.4 | Clinical recommendations

For all PCs used, no negative side effects have been reported. Recommendations are made based on the evidence for clinical benefits taking into consideration the small number of underpowered studies that could be included for individual indications. Hence, the resulting evidence is still weak and the strength of clinical recommendations is low.

In ridge preservation procedures, **PRF** can be used as sole material or in combination with non-autogenous graft material to limit alveolar ridge resorption after dental extraction. The use of **PRP** or **PRGF** in these indications does not appear to be recommendable alone or in combination with graft materials for this indication due to a lack of effect.

The use of **PRF** during implant placement cannot yet be recommended due to limited and premature clinical evidence.

The use of **PRF** and **PRP** in sinus augmentations in combination with grafting materials appears not to be recommendable due to a lack of effect.

The use of **PRF** as an adjunct to open flap debridement in the treatment of peri-implantitis cannot yet be recommended due to limited / premature data.

The use of **PRP** in lateral augmentation procedures may be recommendable but the evidence is low.

1.5 | Recommendations for future research

Future RCTs should:

- be adequately powered with appropriate sample size calculation.
- address implant-related surgical procedures (ridge preservation, implant placement, sinus augmentation techniques, peri-implantitis treatment) to enhance the existing evidence.
- assess potential benefits in locally compromised areas and systemically compromised patients.
- address patient-reported outcome measures (PROMs) (reduction in pain/swelling/oedema).
- include elements of relevant health economics / cost aspects.

2 | WHAT IS THE IMPACT OF TITANIUM PARTICLES AND BIOCORROSION ON IMPLANT SURVIVAL AND COMPLICATIONS? A CRITICAL REVIEW

Titanium is an abundant element in the earth crust, and its salts are widely used in all kinds of products of modern life Thus, every individual living in a developed country is invariably and continually exposed to TiO_2. It is used as micro- or nanoparticles in foods, toothpastes, cosmetics, sunscreens and medicine pills. Nevertheless, concerns have been raised regarding the potential of titanium particles located in peri-implant tissues to induce host reactions that may contribute to complications in dental implant therapy. Micro-particles and nanoparticles differ in their action on the cells. Nanoparticles were described as more biologically reactive and thus potentially more harmful than micro-particles. The purpose of this review was to analyse the current evidence regarding the association between the release of titanium particles and the biological complications of dental implants. In pursuit of this, the following questions were elaborated:

2.1 | What are the potential origins of titanium particles found in peri-implant tissues?

The following mechanisms have been suggested to be involved in the release of titanium particles from surfaces of dental implants: mechanical wear, contact with chemical agents, effects of biofilm adhesion and inflammatory cells.

In vitro and *in vivo* experiments show that particles can be released from surfaces of dental implants in a process called "tribocorrosion." It involves mechanical wear and environmental factors. Mechanical wear occurs during placement of the implants, as a result of micro-motion between implant parts and suprastructures and in the context of mechanical prophylaxis and therapy of mucositis and peri-implantitis.

In vitro studies demonstrate that acidic environments induced by bacterial biofilms and/or inflammatory processes trigger the release of titanium particles, a process referred to as "biocorrosion."

Animal experiments have also shown that particles originating from external sources can accumulate in the gingival tissues irrespective of existing implants.

2.2 | What is the evidence that titanium particles have cytotoxic and/or pro-inflammatory effects?

In vitro experiments assessed effects of titanium ions or particles on bone and soft tissue. Titanium debris can disturb the balance between bone formation and bone resorption in two ways: directly, by differentially activating osteoclasts and osteoblasts, or indirectly, by stimulating the secretion of inflammatory cytokines produced by macrophages and lymphocytes. Epithelial cells and fibroblasts have shown reactivity to titanium particles. Research has also identified factors modulating such effects, notably particle size and association with molecules like LPS.

2.3 | What is the biological plausibility for a link between titanium particles and corrosion in peri-implant tissues and biological complications?

Titanium particles are commonly detected in healthy and diseased peri-implant mucosa alike, and even in gingiva of individuals without titanium implants. Thus, there is poor specificity for the association between the presence of particles and pathology. 15 available studies reporting data on titanium particles in tissues adjacent to dental implants (mucosa overlying titanium cover screws during submerged healing of two-piece implants, mucosa from peri-implantitis lesions, mucosa with marked clinical signs of inflammation, mucosa from implants without clinical signs of pathology, gingiva from healthy teeth) indicate there is a tendency to find more titanium in close proximity of the implant surface and in specimens from diseased sites. However, evidence for a simple cause and effect relationship between titanium particles and biological implant complications does not exist. *In vitro* experiments demonstrate that titanium particles can interfere with cell function, possibly promoting inflammation under some circumstances. Moreover, release of titanium particles in acidic environments induced by bacterial biofilms and/or inflammatory processes have been shown *in vitro*. The true impact of these findings on patients with titanium implants, however, is not determined.

2.4 | What is the evidence for hypersensitivity to titanium?

The evidence for existence of hypersensitivity against titanium is weak. It consists essentially in a limited number of cases where a temporal association between exposure to titanium and occurrence of tissue reactions could be demonstrated, and in finding such

reactions in tissues in proximity to implanted titanium. There is no consistency in findings observed by different persons in different places with different samples. Also, there is poor specificity as the observed reactions could be caused by other factors associated with the placement of implants. Coherence between epidemiological and laboratory findings consists in two studies presenting results from selected populations.

2.5 | What is the evidence for advocating the use of hypersensitivity testing in the context of treatment planning?

The validity of patch testing is questionable because it evaluates reactions to epidermal rather than oral mucosal contact. Oral mucosa and skin have different permeability and immunological properties, as reflected in the number of antigen-presenting cells. There is controversy about the validity of lymphocyte immuno-stimulation assays, especially with regards to the unclear rate of false-positive results.

Studies showing clinical utility are missing. Test positive and negative patients treated with titanium or non-titanium implants should be monitored prospectively to assess the differential incidence of biological complications.

2.6 | What is the evidence that the presence of titanium particles has an impact on implant survival/success and biological complications?

In terms of multiple and/or recurrent non-integration, or spontaneous loss of osseointegration, there is no direct evidence that titanium particles have an impact on implant survival/success. Aseptic loosening has not been limited to titanium implants but has been reported for zirconia implants alike.

For peri-implantitis, it has been suggested that the incidence is lower for zirconia than titanium implants. However, robust data from prospective studies to confirm this are currently unavailable.

Although all currently available protocols for therapy of mucositis and peri-implantitis further contaminate the peri-implant tissues with titanium particles, they have a certain degree of success. Some protocols even include the placement of titanium granules for the treatment of peri-implantitis lesions.

Hence, based on the current level of evidence, and the small number of reported cases, it is unlikely that adverse biological reactions elicited by titanium play a major role in the aetiology of peri-implant diseases.

2.7 | Clinical recommendations

Current evidence does not suggest that there is an increased risk of an adverse effect of titanium particles that would reason considerations for implant material selection other than titanium.

There is insufficient evidence to recommend immunological testing related to implant material for planning and monitoring of implant therapy.

2.8 | Recommendations for research

Future research should:

- develop appropriate animal models to explore the effects of artificial contamination of peri-implant tissues with titanium particles for *in vivo* research.
- assess immunological and tissue reactions to placement of titanium and non-titanium implants and prospective monitoring of peri-implant tissue conditions.
- perform prospective monitoring of immunological and tissue reactions to implant placement in relation to immunological risk factors

3 | THE EFFECT OF ANTIRESORPTIVE DRUGS ON IMPLANT THERAPY: A SYSTEMATIC REVIEW

Antiresorptive drugs (ARDs) are used predominantly for the treatment of osteoporosis and management of skeletal metastases of malignancies, to prevent events like fractures, and limit pain and metastatic spread. Use of ARDs has traditionally been divided according to the route of administration (i.e. oral, subcutaneous, intravenous). Current understanding, however, is that dose rather than route of administration is important. Thus, low- and high-dose ARDs can be today administered through all three routes. Primarily, low-dose is used for osteoporosis treatment, whereas high-dose is used in cancer patients with bone metastases. Patients on ARD have a risk of developing medication-related osteonecrosis of the jaw (MRONJ), a specific complication directly related to this type of drugs that can have devastating consequences for the individual patient.

Herein, 24 studies including ≥ 10 patients with bisphosphonate (BP) intake (mainly low-dose for osteoporosis treatment) and control patients not taking BP were identified. Collectively, some type of information was provided regarding: implant success, failure, or loss, in 23 studies; bone grafting procedures in 11 studies; MRONJ in 17 studies; peri-implantitis in 9 studies. Precise figures were reported regarding: a) implant loss in 12 studies on patient level (1218 BP patients; 1144 controls) and in 15 studies on the implant level (2849 implants in BP patients; 3946 implants in controls); b) grafting procedures in 6 studies on implant/site level (336 BP patients); c) MRONJ associated with implants in 16 studies on patient level (1390 BP patients). In addition, 7 case series on implant-associated MRONJ including 11 to 27 patients were identified (116 in total).

The major bulk of evidence on ARD intake in implant therapy derives from studies reporting on low-dose oral BPs. There are limited data on possible detrimental effects of high-dose BPs and newer type

ARDs (e.g. denosumab) in conjunction with implant therapy. It is important to note that the evidence of this report is limited due to the fact that it derives from studies with low quality in terms of design, quality of reporting and number of included cases and/or controls.

To address the large number of possible combinations of different ARDs and ARD dosages, routes of administration as well as timing of implant placement / start of ARD therapy, the following questions were handled separately:

3.1 | Are implant placement and/or bone augmentation procedures associated with increased risk of implant loss or other complications in osteoporosis patients on low-dose ARD intake?

The currently available evidence indicates that patients on low-dose oral BP do not lose more implants nor get more implant-related complications (i.e. peri-implant marginal bone loss, peri-implantitis) compared to implant patients without BP intake. Implant loss in patients on low-dose BP has been reported in few studies, and these were predominantly early losses (i.e. within short time post-installation/post-loading). The available knowledge regarding success or safety of bone grafting procedures in conjunction with implant installation is too limited to draw conclusions.

It has to be kept in mind that all patients on low-dose ARD (BP and denosumab) intake, including implant patients, do have a risk of MRONJ. MRONJ in association with implant therapy has been reported to occur within a short timeframe of weeks (i.e. implant surgery was assumed as the trigger) to several years after implant installation, even in the case of low-dose oral BP intake. The incidence of MRONJ in implant patients on low-dose oral BP is currently unknown, albeit it appears to be low.

3.2 | Does low-dose oral BP intake in osteoporosis patients compromise the longevity of existing implants?

There is no evidence that low-dose oral BP intake compromises the longevity of existing implants. However, based on case series, there is evidence that MRONJ may appear associated with implants in patients with low-dose oral BP intake, resulting in implant loss. The incidence of implant-associated MRONJ in these patients is currently unknown, albeit it appears to be low.

3.3 | Does low-dose subcutaneous or intravenous ARD administration in osteoporosis patients have an impact on the outcome of implant therapy in terms of implant losses and/or complications?

There is insufficient data to draw conclusions on the possible effect of low-dose subcutaneous and intravenous ARD administration on the outcome of implant placement or pre-existing implants in osteoporosis patients.

3.4 | Does duration of low-dose ARD intake in osteoporosis patients have an impact on the outcome of implant therapy in terms of implant losses and/or complications?

The risk of MRONJ in all patients on low-dose ARD (BP and denosumab) intake increases with increased duration of intake. Based on currently available data, the effect of the duration of low-dose ARD intake in implant patients on the risk of implant loss or the development of implant-associated MRONJ is unclear. Six studies on single-patient data reported that MRONJ associated with implants in patients on BP for osteoporosis appeared mainly >36 months after start of drug intake (in 29 out of 41 patients; 71%).

3.5 | Does ARD dose (low vs. high) have an impact on the outcome of implant therapy in terms of implant losses and/or complications?

Based on currently available data, the effect of dose on the survival of implants placed in patients with ARD intake is unclear. In general, the risk of MRONJ is higher in cancer patients on high-dose ARD than in osteoporosis patients on low-dose ARD (BP and denosumab). Data from 6 studies on single-patient data show MRONJ appearing in cancer patients MRONJ mainly ≤ 36 months of BP intake (20 out of 32 patients; 64%), whereas it occurred in patients on BP for mainly >36 months after start of drug intake (in 29 out of 41 patients; 71%).

3.6 | Does the interruption of ARD intake ("drug holiday") have an impact on the outcome of implant therapy in terms of implant losses and/or complications?

A "drug holiday" has been recommended in some published clinical guidelines. However, due to the lack of evidence, the benefits of this concept in implant therapy remain unclear.

3.7 | Consensus statements

- Implant therapy in patients receiving low-dose oral BP for osteoporosis treatment is not associated with an increased risk of implant loss or other complications compared to patients without BP intake.
- Current knowledge on the effect of low-dose subcutaneous and intravenous ARD administration on implant therapy is insufficient to draw conclusions.
- Patients on low- and high-dose ARD are at risk of developing MRONJ irrespective of implant therapy. The risk of MRONJ increases with dose and duration of ARD intake. The incidence of implant-associated MRONJ in patients on low-dose ARD (BP and denosumab) is currently unknown, albeit it appears to be low.
- The benefits of the "drug holiday" concept in implant therapy are unclear.

3.8 | Clinical recommendations

- Low-dose oral BP intake for osteoporosis treatment per se is not a contraindication for implant installation. There are no data on low-dose subcutaneous and intravenous ARD intake in conjunction with implant therapy to draw conclusions. However, based on epidemiological data, there is no reason to assume a higher risk of complications in these groups of ARD compared to low-dose oral BP intake.
- Currently, no recommendations can be given on bone grafting procedures in conjunction with implant therapy in patients on low-dose ARDs. Individual patient assessment with a focus on known risk factors is mandatory, for example local factors, smoking, systemic diseases, comedications and duration of ARD intake.
- Based on information from tooth extraction studies on patients with high-dose ARD intake, measures for primary intention healing (e.g. submerged implants), including prophylactic use of antibiotics and postoperative antiseptics (e.g. chlorhexidine), is recommended when implant therapy and/or bone grafting procedures are performed in patients with low-dose ARD intake.
- A drug holiday should be only considered after consultation with the treating physician.
- Implant therapy and/or bone grafting procedures are currently not recommended in patients on high-dose ARD intake.

3.9 | Future research

Future research should:

- evaluate the potential benefits of prophylactic use of antibiotics in association with implant installation and/or bone augmentation procedures in patients with low-dose ARD intake.
- evaluate the potential benefits of a drug holiday in association with implant installation and/or bone augmentation procedures in patients with low-dose ARD intake.
- explore the potential for implant therapy in patients on high-dose ARD in particular in comparison with alternative modes of treatment (removable prostheses) that can give rise to the occurrence of MRONJ themselves.

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REFERENCES

Stähli, A., Strauss, F. J., & Gruber, R. (2018). The use of platelet-rich-plasma to enhance the outcomes of implant-related therapies: A systematic review. *Clinical Oral Implants Research*, *29*(Suppl. 18), 6-19. https://doi.org/10.1111/clr.13275.

Mombelli, A., Hashim, D., & Cionca, N. (2018). What is the impact of titanium particles and bio-corrosion on implant survival and complications? A critical review. *Clinical Oral Implants Research*, *29*(Suppl. 18), 37-53.

Stavropoulos, A., Bertl, K., Pietschmann, P., Pandis, N., Schiødt, Morten, & Klinge, B. (2018). The effect of antiresorptive drugs on implant therapy: A systematic review. *Clinical Oral Implants Research*, *29*(Suppl. 18), 54-92.

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